Cohort Study

ANNALS OF MEDICINE & SURGERY

OPEN

Primary gastrointestinal non-Hodgkin lymphoma: a retrospective study in Vietnam

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Background: Although primary gastrointestinal non-Hodgkin lymphoma (GI NHL) is a rare hematopoietic malignancy, it is the most common extranodal site involved by lymphoma. Treatment methods are chosen based on many factors, including site of lesion, histopathology, symptoms, and patients' choice.

Objectives: To evaluate the clinical characteristics, treatment results and prognosis for primary GI NHL in Vietnamese patients.

Patients and methods: This was a retrospective descriptive study on 126 patients with primary GI NHL treated at our hospital from 2010 to 2015. Data of all patients were collected and analyzed.

Results: B-cell non-Hodgkin's lymphoma was the major pathology with rate of 93.7%, in which Diffuse Large B-Cell Lymphoma type accounted for 58.7%, followed by Mucosa-associated lymphoid tissue lymphoma type 22.2%. Less common forms were cystic type, Burkitt's lymphoma, Mantle cell, T cell. The majority of patients receiving chemotherapy achieved a complete response, up to 70%. Overall survival and 5-year disease-free survival were 74.1% and 59.3%, respectively. Overall, stomach lymphoma had a longer survival rate than those in the small intestine. Factors including Eastern Cooperative Oncology Group score of 2–4, elevated Lactate Dehydrogenase levels at baseline, stage of widespread illness (III/IV), high malignancy histopathology, and lesion size of more than 10 cm were poor prognostic indicators.

Conclusions: Gastric lesion was the most frequent site and has better prognosis than other locations. Other prognostic factors for overall survival included Eastern Cooperative Oncology Group score, Lactate Dehydrogenase levels, stage, histopathology, and lesion size.

Keywords: gastrointestinal tract, hematopoietic malignancy, non-Hodgkin lymphoma, primary, Vietnam

Introduction

Primary gastrointestinal non-Hodgkin lymphoma (GI NHL) arises from Peyer's plaques or lymphocytes of the stomach or colon mucosa. While the illness accounts for 1–10% of all gastrointestinal cancers and 4–20% of non-Hodgkin lymphoma in general, this is the most prevalent extranodal location, with percentage of 40–60%[1]. Primary GI NHL may develop anywhere in the gastrointestinal system, with the stomach being the most frequent site, followed by the small intestine and ileocecal area[2]. Histologically, 90% of primary GI NHL are B-cell lymphomas, and rarely T-cell lymphomas[3]. Currently, the pathophysiology of primary GI NHL is still unknown. According to several publications, it may be related to the infection with H. pylori, HIV, C. jejuni, EBV, HTLV-1, or non-infectious disorders of the urinary tract bowel, or autoimmune disease[4,5].

Treatments on primary GI NHL are still controversial. The general treatment strategy is systemic chemotherapy combined with locoregional therapies such as radiation or surgery[1,2]. Surgical treatment is usually indicated for intestine lymphomas, especially in cases of bowel obstruction or perforation[6]. Helicobacter pylori eradication is the first-line treatment of gastric mucosa-associated lymphoid tissue lymphoma in patients with Helicobacter pylori infection[7]. Radiotherapy is often used in cases with residual lesions or pre-treated bulky tumours[2].

Due to the rarity of this disease, its distinct diagnosis and treatment plan, to our best knowledge, there are still relatively few studies focusing on a comprehensive analysis of non-Hodgkin lymphoma involving the gastrointestinal tract, especially in Vietnam. Moreover, other report found that regarding

HIGHLIGHTS

- Gastrointestinal non-Hodgkin lymphoma had high complete response rate with chemotherapy.
- Gastric lesion was the most frequent site and had better prognosis than others.
- Prognostic factors included Eastern Cooperative Oncology Group, Lactate Dehydrogenase levels, stage, histopathology, and lesion size.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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Annals of Medicine & Surgery (2023) 85:2390–2394

Received 30 March 2023; Accepted 10 May 2023

Published online 17 May 2023

http://dx.doi.org/10.1097/MS9.0000000000000858

cancer outcomes in general, the majority of Vietnamese patients with cancer appeared for treatment at late stages and experienced poor survival rates[8]. Therefore, this study aimed to evaluate the distinguished characteristics including frequency of affected sites and histological classification, as well as the treatment outcomes in both short-term and long-term aspects of primary GI NHL among Vietnamese patients.

Materials and methods

Study design

This was a retrospective analysis in patients with primary GI NHL treated in our hospital from 2010 to 2015.

Study participants

There were 126 primary GI NHL patients treated at our hospital between 2010 and 2015 recruited. Patients were diagnosed based on the Dawson criteria, significant intestinal lesions with or without regional lymph nodes, without peripheral lymphadenopathy at the time of diagnosis, no mediastinal enlargement, white blood cell count within normal limits, and no involvement of the liver or spleen. Exclusion criteria included paediatric patients (< 16 years old), recurrent primary GI NKL, and lymphoma in the lymph nodes that spread into the gastrointestinal tract.

After eligible patients were selected, their clinical and laboratory parameters were documented, as well as their surgery, chemotherapy, and radiation treatment information. Evaluation of response based on WHO criteria, adverse events, progression-free survival, and five-year survival were also collected.

Data analysis and statistical method

Data were collected, processed, and analyzed on SPSS 20.0 software. The data were presented as mean, SD, frequency, and percentage. The $\chi 2$ test was utilized when comparing rates, with 95% CI. Survival was estimated by the Kaplan–Meier method and compared by the log-rank test. A significance level of P less than 0.05 was used.

All participants have given informed written consent. The work has been reported in line with the STROCSS criteria[9].

Registration and ethics: Research Registry number is stated, in accordance with the declaration of Helsinki.

Result

Clinical features

The characteristics of patients in our study were presented in Table 1. Among 126 patients in our study, 85% of patients were above the age of 40, with average age of 53 years old, in which the male/female ratio was 1.3:1. In general, patients often admitted to the hospital between three to 6 months following the onset of symptoms. In which, abdominal pain was the most common symptom (83.3%). There were 35 patients who presented to the hospital in emergency conditions, including gastrointestinal haemorrhage, intestinal obstruction, and B syndrome. It is found that the most frequent tumour location was stomach (51.6%), followed by colon site (23.8%). Although there were six patients (5.1%) having bone marrow infiltrates which referred to advanced stage, the majority of patients (69%) had tumours less than 10 cm in size.

In terms of histological classification, B-cell non-Hodgkin's lymphoma was the major pathology with rate of 93.7%, in which Diffuse Large B-Cell Lymphoma type accounted for 58.7%, followed by Mucosa-associated lymphoid tissue lymphoma (MALT) type 22.2%. Less common forms were cystic type, Burkitt's lymphoma, Mantle cell, T cell with only 6 patients (6.3%). The localized stage (stage I/II) accounted for 65.1%, while stage III with involved lymph node in both sides of the diaphragm was 22.2% and the disseminated stage (stage IV) was 12.7%.

Table 1

Characteristics of study patients.

Patients' characteristics	Value ($n = 126$)
Sex	
Male	72 (57.1)[a]
Female	54 (42.9)[a]
Age (year)	53.0 ± 12.3[b]
Time from symptom onset to hospital admission (month)	
< 3	36 (28.6)[a]
3–6	52 (41.3)[a]
> 6	38 (30.1)[a]
Clinical symptoms	
Weight loss	62 (49.2)[a]
Anaemia	51 (40.5)[a]
Abdominal pain	105 (83.3)[a]
Nausea and vomiting	56 (44.4)[a]
Diarrhoea	26 (20.6)[a]
Constipation	22 (17.5)[a]
Gastrointestinal bleeding	17 (13.5)[a]
Bowel obstruction	14 (11.1)[a]
Perforation	4 (3.2)[a]
Palpable tumour	19 (15.1)[a]
B syndrome	43 (34.1)[a]
Location of lesion	
Stomach	65 (51.6)[a]
Small intestine	21 (16.7)[a]
Colorectal	30 (23.8)[a]
Multiple locations	10 (7.9)[a]
Size of lesion	
> 10 cm	39 (31)a
< 10 cm	87 (69)a
Condition of marrow	
Marrow infiltration	6 (5.1)[a]
No marrow infiltration	120 (94.9)[a]
Lugano clinical stage	
I	38 (30.2)[a]
II	44 (34.9)[a]
III	28 (22.2)[a]
IV	16 (12.7)[a]
Histopathology	
Low malignancy	
MALT	28 (22.2)[a]
FL	5 (4.0)[a]
High malignancy	
DLBCL	74 (58.7)[a]
Burkitt	6 (4.8)[a]
Mantle cell	5 (4.0)[a]
T cell	8 (6.3)[a]

[a]Data were presented as *N* (%).
[b]Data were presented as mean ± SD.
DLBCL indicate Diffuse Large B-Cell Lymphoma; MALT, Mucosa-associated lymphoid tissue lymphoma; FL, Follicular lymphoma

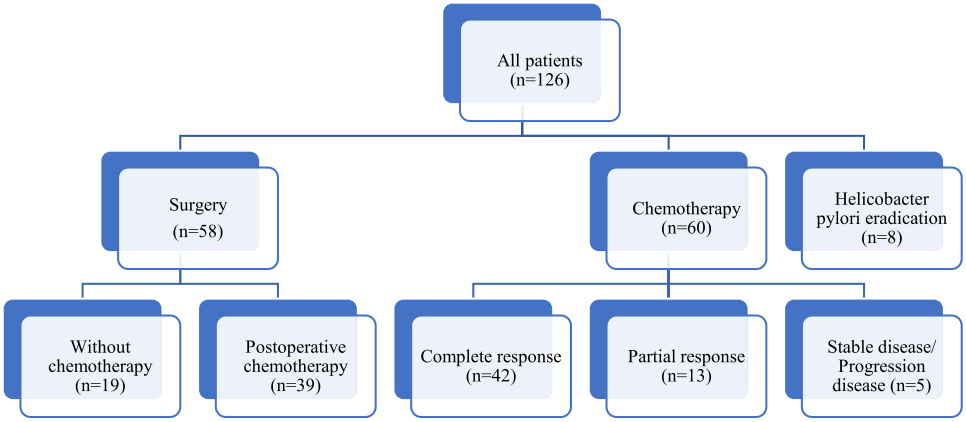

Figure 1. Flow diagram of patients' treatments and responses.

Treatment results

Patients' treatment and response were presented in Figure 1. In this study, 58 patients underwent surgery for total tumour resection (46.1%), in which, 39 patients received postoperative chemotherapy (31%). On the other hand, 60 patients (47.6%) had chemotherapy as initial treatment. Only eight patients were treated with Helicobacter Pylori eradication alone. The majority of chemotherapy patients (70%) obtained a complete response to treatment.

The 5-year disease-free survival (DFS) and overall survival (OS) rates were 59.3% and 74.1%, respectively. The 5-year survival rate for individuals with gastric lesions was 87.7%, compared to 65.0% for those with small intestinal lesions. The difference was statistically significant ($P = 0.043$). Patients with primary GI NHL had different survival rates based on their histopathology features ($P = 0.04$). The 5-year survival rate for individuals with low-grade malignancy was 78.6%, compared with 48.5% for those with high-grade histopathology. Moreover, patients with local stage (stage I/II) had a significantly greater 5-year survival rate than those with disseminated stage (stage III/IV) (90.4% vs. 44.6%, $P < 0.01$). Patients who obtained a complete response had a significantly greater 5-year survival rate than those who did not (86.2% vs. 59.4%, $P = 0.04$). Survival prognostic factors in the study group included high Lactate Dehydrogenase (LDH) concentration, Eastern Cooperative Oncology Group (ECOG) score greater than or equal to 2, and lesion size over 10 cm. In contrast, there was no difference in survival between the age group above and below 60 years, sex, and with or without B syndrome (Table 2).

Discussion

GI NHL is a kind of relatively rare malignancies compared with other cancer in the alimentary tract, with distinguished characteristics and treatment. Koch *et al.*[10] analyzed sites of organ with 317 patients with primary GI NHL, in which the most common location was the stomach (74.7%) and the second leading group was the small intestinal. Other author found the number of patients with primary gastric lymphoma and primary intestinal lymphoma being almost equal distribution[11]. Our study showed that gastric region accounted for a half of patients, being comparable to the latter report.

In our study, 58 patients had surgical excision of lesions, with the majority receiving postoperative chemotherapy. 19 patients who got surgery alone were recommended for chemotherapy but declined the treatment. In contrast, chemotherapy alone accounted for 47.6% of cases. It was fact that not many patients with primary GI NHL received it in the past. From 1991 to 2001, only 8% of patients with primary GI NHL in southern China got chemotherapy alone. However, from 2002 to 2012, the incidence of chemotherapy alone increased to 37.3%[12]. The complete response rate of chemotherapy in patients with primary GI NHL

Table 2

Relationship between overall survival and some prognostic factors

	N	5-year OS	*P*[a]
Location of lesion			
Stomach	65	87.7	**0.043**
Small intestine	21	65.0	
Histopathology			
Low-grade	33	78.6	**0.04**
High-grade	93	48.5	
Stage			
I/II	82	90.4	**< 0.01**
III/IV	44	44.6	
LDH concentration level			
Normal	59	83.0	**0.032**
High	41	58.4	
ECOG score			
0–1	66	81.3	**0.02**
2–4	34	45.4	
Age			
< 60	72	73.4	0.23
≥ 60	28	67.7	
Sex			
Male	73	74.8	0.57
Female	54	72.4	
Size of lesion			
< 10 cm	87	80.4	**0.012**
≥ 10 cm	39	44.7	
B syndrome			
With	62	75.6	0.19
Without	38	62.9	

[a]Statistically significant on univariate analysis, *P*-value less than 0.05.
OS indicate overall survival; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate Dehydrogenase.

in our study was 70%, whereas the partial response rate was 21.7%, no response or progression rate was 8.3%. Based on the site of the lesion, we found that the rate of complete response in the stomach was 77.4%, which was slightly higher than the rate in the small intestine, which was 65.0%, but the difference was not statistically significant ($P = 0.37$). In a study of Papaxoinis with 128 cases of primary GI NHL, the complete response rate was as high as 80% in the chemotherapy group[13]. Avilés et al evaluated the response in patients with non-Hodgkin lymphoma in the stomach, the overall complete response rate was 91%, with the complete response rate being 91% for surgery plus chemotherapy, and 93% for chemotherapy alone; there was no difference in response between treatments ($P = 0.866$)[14]. Moreover, in the small intestine lymphoma cases, Seo K observed a 64.4% complete response rate among chemotherapy patients[15]. Thus, chemotherapy played a main role in treatment strategy of primary GI NHL. On the other hand, localized, favourable histopathology of the non-Hodgkin lymphoma in the lymph nodes may be cured with radiotherapy. In the gastrointestinal system, radiation was mostly employed for stomach MALT tumours and isolated rectal lesions[2]. In other cases, radiation therapy was effective but must be combined with chemotherapy. There was no subject in this study getting radiation alone. Four patients received radiation treatment for residual lesions after chemotherapy (one case in the stomach and three cases in the rectum).

In 1995, Helicobacter pylori antibiotic resistance were first used to treat stomach MALT tumours in patients with stage IE, low-grade MALT tumours[7]. In 2013, Isaacson and Du reported more than 550 cases from different centres worldwide had confirmed that 75% gastric MALToma could be successfully treated with antibiotics[16]. However, some patients were refractory, thus the effectiveness of radiotherapy for MALToma refractory to H. pylori eradication had been demonstrated[17]. Schechter and Yahalom indicated that 17 gastric MALToma patients with stage I–II were treated with radiation therapy to stomach and perigastric lymph nodes. The median of total radiation dose was 30 Gy and all patients obtained complete response[18]. In our research, eight patients with stomach MALT tumours were treated to eliminate H. pylori bacteria. Due to a misdiagnosis at the first endoscopic biopsy, a negative H. pylori test, or a later stage, the remaining cases with MALT tumours were surgically or chemotherapeutically plus surgically treated with postoperative histopathology as MALT tumour.

In this study, the OS time of patients with non-Hodgkin lymphoma in the stomach was better than with small bowel lesions or multisite lesions ($P = 0.015$). There was a difference in survival according to histopathological characteristics in patients with primary GI NHL ($P = 0.046$). The 5-year OS in the group of patients with low-malignant histopathology was 78.6%, and 48.5% with high-malignant histopathology. In addition, patients with the local stage (stage I/II) had better survival time, the 5-year survival rate was higher than that of the disseminated stage group (stage III/IV) (90.4% vs. 44.6%, $P < 0.01$). This result was also consistent with the study of Minrui Li, 5-year OS and DFS of 104 patients were 56.4% and 49.3%, respectively. In which, OS and DFS of the gastric group (72.3% and 48.4%) were higher than those with lesions in the small intestine (43.1% and 23.6%)[12]. Moreover, histopathology features closely related to survival also have been confirmed in many studies around the world. Tong Wang compared survival according to histopathology and found that the survival rate of high malignancy group (Diffuse Large B-Cell Lymphoma) was lower than that of the low malignancy (MALT) group (OS: 55% vs. 78%, $P < 0.01$)[11]. Besides, according to Papaxoinis's study, the early clinical stage had a better survival time of 3 years than the late clinical stage (3-year survival: 87% vs. 60%, $P < 0.001$)[13].

Rather than tumour location, histological type, and stage, our study also found that high LDH concentration and ECOG score greater than or equal to 2 were poor prognostic factors. In the study of Li *et al*.[12], by using multivariate analysis, he indicated that patients with good performance status and normal LDH had better survival. Other studies also supported performance status and LDH as independent factors[11,19,20]. Besides, bulky mass, being usually defined as lesion of 10 cm or more in the longest diameter, was also considered as a poor prognostic factor in lymphoma[21–23]. In our study, although fewer patients were associated with bulky disease, there was still a relationship between lesion size over 10 cm and survival.

There were several potential limitations in our study. As a retrospective analysis and single arm study, which might reduce its statistical power and impact the results. Due to a small number of patients, it could not be adequately representative or have appropriately balanced groups to minimize the effect of confounding factors. In addition, assessment of which optimal regimen of adjuvant setting was not well placed in this study.

Conclusion

Our data from our hospital showed that Primary GI NHL was very uncommon and had distinguished characteristics, treatment, and prognosis to nodal lymphoma. Gastric lesion was the most frequent site and has better prognosis than other locations. Factors including ECOG score of 2–4, elevated LDH levels at baseline, stage of widespread illness (III/IV), high malignancy histopathology, and lesion size of more than 10 cm were poor prognostic indicators.

Ethical approval and consent

The project was approved by ethical board. The publication of this study has been consented by all patients.

Source of funding

No funding sources.

Author contribution

T.T., H.Q.V. Designed the study, did the data collection, the data analysis, the writing paper. T.H.V., H.T.N., H.V.N. collected data, revised the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of interest disclosure

None.

Research registration unique identifying number (UIN)

1. Name of the registry: Research Registry 2. Unique Identifying number or registration ID: researchregistry8873 3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-theregistry#home/registrationdetails/6441dbbfc3d41e0027084b95/.

Guarantor

Dr. Thang Tran.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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